NTP
National Toxicology Program

Draft NTP Monograph on Health Effects of Low-level Lead:

Reproductive and Developmental Effects

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Reproductive and Developmental Effects of Pb

- Principal health effects of Pb
  - **Children**
    - Growth and puberty
  - **Adults**
    - Sperm and conception at higher blood Pb levels
    - Some studies report association with fetal growth, pregnancy loss, gestation length
- ATSDR and EPA conclude
  - Effects on sperm and fertility at higher blood Pb (>10µg/dL)
  - Limited and mixed results for reproductive effects in females
- Animal data - reproductive and developmental toxicity of Pb

Reproductive and Developmental Effects

Table 8.1: Major reproductive/developmental effects considered	
Effect	**Description**
Delayed puberty	Delay in measures of puberty (e.g., Tanner genital, pubic hair, and breast staging)
Postnatal growth	Slower growth (as indicated by height, head circumference, etc. for age)
Sperm parameters	Numerous sperm or semen measures (sperm count, motility, morphology)
Conception	Greater time to pregnancy or lower fecundity
Pregnancy loss	Spontaneous abortion (fetal loss<20 weeks gestation), Stillbirth (fetal loss ≥20 weeks)
Gestation length	Shorter gestation length (continuous measure) / preterm birth (<37 weeks)
Fetal growth	Lower birth weight, often adjusted for gestational age
Birth defects	Congenital malformations

Puberty

- Delay or puberty occurring at later age
- Indications of puberty include
  - Tanner staging of genital, pubic hair, or breasts
  - Age at menarche

NTP Conclusions: *sufficient* evidence that blood Pb levels <10µg/dL are associated with delay in puberty onset in children

And *limited* evidence of an association in children with blood Pb levels <5µg/dL

Puberty - Evidence

NTP Conclusions: *sufficient* evidence <10µg/dL and *limited* evidence <5µg/dL based on:

- 7 cross-sectional studies and a prospective study
  - Association between blood Pb and delayed appearance of biomarkers of puberty
  - Children with mean Pb levels from <1 to <10µg/dL
- Mixed results at mean blood Pb levels <5µg/dL

- **Supported by**
  - Similar results at blood Pb ≥10µg/dL (Tomoum, 2010)
  - Animal data on Pb-associated delay in sexual maturation

Postnatal Growth

- Slower growth as indicated by height, head circumference and other measures adjusted for age of the child

NTP Conclusions: *sufficient* evidence that blood Pb levels <10µg/dL in children are associated with decreased growth

and *limited* evidence that maternal blood Pb levels <10µg/dL are associated with decreased head circumference in children up to age 4

Postnatal Growth - Child Blood Pb Evidence

NTP Conclusions: *sufficient* evidence <10µg/dL based on:

- Several prospective studies reporting decreased growth with early childhood blood Pb levels <10µg/dL (Green and Ernhart, 1991; Rothenberg, 1993; Rothenberg, 1999)
- Numerous cross-sectional studies with blood Pb <10µg/dL
- **Supported by**
  - Similar effects in children at higher blood Pb levels >10µg/dL (e.g., Kordas, 2004; Little, 2009)
  - Animal data on Pb-associated decreased growth rate

Postnatal Growth - Prenatal Pb Evidence

NTP Conclusions: *limited* evidence that maternal blood Pb <10µg/dL is associated with decreased head circumference based on:

- Several prospective studies reporting decreased head circumference in children associated with maternal blood Pb levels <10µg/dL (Rothenberg, 1993; Rothenberg, 1999; Schell, 2009)
- No association with child height
- **Supported by**
  - Animal data on Pb-associated decreased growth rate with prenatal exposure

Sperm or Semen

- Pb-related effects on sperm or semen include:
  - Lower sperm numbers, decreased motility, reduced semen volume, and increased percentage of sperm with abnormal morphology

NTP Conclusions: *sufficient* evidence that blood Pb levels ≥15µg/dL is associated with adverse effects on sperm or semen in adult men

and *inadequate* evidence at blood Pb levels <15µg/dL

Sperm or Semen - Evidence

NTP Conclusions: *sufficient* evidence ≥15µg/dL based on:

- Multiple retrospective and cross-sectional studies reporting associations with blood Pb levels from 15 to 68µg/dL
  - 7 studies support threshold of ≥40µg/dL
    - Few individuals with blood Pb <10µg/dL (except: Bonde, 2002; Kasperczyk, 2008)
    - Limited ability to detect effects at lower doses
  - 4 studies support lower threshold of 15 to 31µg/dL
    - 15µg/dL (Naha, 2005)
    - 20µg/dL (DeRosa, 2003)
    - 25µg/dL (Telisman, 2000)
    - 31µg/dL (Mahmoud, 2005)
  - Individuals attending infertility or IVF clinics
    - Mixed results report effects below 10µg/dL
- **Supported by**
  - Animal data on Pb-associated sperm effects

Fertility / Delayed Conception Time

- Delayed conception time
  - Time to pregnancy
- Decreased fertility
  - Odds of conception over a given time (fecundability)

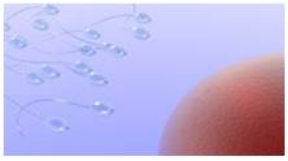
NTP Conclusions:

Men:

(1) *sufficient* evidence that paternal blood Pb ≥20µg/dL is associated with delayed conception time, and

(2) *limited* evidence at blood Pb ≥10µg/dL is associated with other measures of reduced fertility

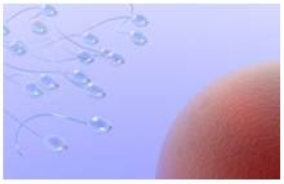
Women: *inadequate* evidence for maternal blood Pb levels <10µg/dL



Fertility / Delayed Conception Time – Evidence in Men

NTP Conclusions: *sufficient* evidence ≥20µg/dL and *limited* evidence ≥10µg/dL in men based on:

- Multiple retrospective and cross-sectional studies
  - 5 studies support greater time to pregnancy or reduced fertility at blood Pb levels of 20, 30, 31, 40, and 46µg/dL
  - 1 large retrospective study reports increased odds ratio of infertility at blood Pb level of 10µg/dL (n=4146; Sallmen, 2000)
- **Supported by**
  - Adverse effects on sperm at similar Pb levels
  - Animal data on Pb-associated increased time to birth and infertility
- **Note**
  - 3 studies report no association with blood Pb (Selevan, 1984; Bonde and Kolstad, 1997; Joffe, 2003)



Spontaneous Abortion

- Spontaneous Abortion:
  - Fetal loss <20 weeks of gestation

NTP Conclusions:

Women: *limited* evidence that maternal blood Pb levels <10µg/dL are associated with spontaneous abortion

Men: *limited* evidence that paternal blood Pb levels >31µg/dL are associated with spontaneous abortion

Spontaneous Abortion – Evidence

NTP Conclusions:

Women: *limited* evidence <10µg/dL, and
Men: *limited* evidence ≥31µg/dL based on:

- **Women**
  - Single prospective nested case-control study (Borja-Aburto, 1999)
  - Mixed evidence at blood Pb levels from 4 to 16µg/dL
  - Supported by:
    - Occupational exposure studies lacking blood Pb data
    - Association with plasma Pb in study lacking blood Pb data (Yin, 2008)
    - Review concluding consistent effects at high blood Pb (Hertz-Picciotto, 2000)
    - Animal data
- **Men**
  - Single retrospective nested case-control study (Lindholm, 1991a,b)
  - Mixed evidence at blood Pb levels from 25 to 60µg/dL

Fetal Growth / Lower Birth Weight

- Several measures of reduced prenatal growth or intrauterine growth retardation
  - Small for gestational age (below 10th percentile)
  - Lower birth weight (continuous variable)
  - Low birth weight (<2500g after 37 weeks gestation)
  - Low birth weight adjusted for gestation length
- Any indication of reduced fetal growth considered

NTP Conclusions:

Women: *sufficient* evidence that maternal blood Pb levels of <10µg/dL are associated with reduced fetal growth and lower birth weight

Men: *inadequate* evidence for paternal blood Pb

Fetal Growth / Lower Birth Weight – Evidence in Women

- **NTP Conclusions**: *sufficient* evidence <10µg/dL based on:
- Multiple prospective, retrospective, cross-sectional studies
  - **4 prospective studies:** maternal blood Pb<10µg/dL during pregnancy (Bornschein, 1989; Dietrich, 1987; Jelliffe-Pawlowski, 2006; Gundacker, 2010)
  - **Multiple cross-sectional studies**: maternal, cord Pb<10µg/dL at birth
  - **1 large retrospective cohort study**: n = 43,238 (Zhu, 2010)
- **Supported by**
  - Association with maternal bone Pb
  - Animal data on Pb-associated lower birth weight
- **Note:** no effect of Pb in 1 prospective and several cross-sectional studies with blood Pb <10µg/dL
  - Also, mixed results at higher blood Pb levels

Preterm Birth / Gestational Age

- Preterm Birth
  - Less than 37 weeks of gestation
- Reduced gestational age
  - Continuous measure of gestation length

NTP Conclusions:

Women: *limited* evidence that maternal blood Pb levels of <10µg/dL are associated with preterm birth or reduced gestational age

Men: *inadequate* evidence

Preterm Birth / Gestational Age – Evidence in Women

- **NTP Conclusions**: *limited* evidence <10µg/dL based on:
- Multiple prospective and cross-sectional studies
  - **2 prospective studies:** maternal blood Pb<10µg/dL during pregnancy (Cantonwine, 2010; Vigeh, 2011)
  - **5 cross-sectional studies**: maternal, cord Pb<10µg/dL at birth
- **Note:**
  No effect of Pb in multiple prospective, retrospective and cross-sectional studies with blood Pb <10µg/dL
  - **1 large retrospective cohort study**: n = 43,238 (Zhu, 2010)
  - Also, mixed results at higher blood Pb levels
  - Animal data not located to support Pb-related preterm birth

Other Reproductive Effects

NTP Conclusion: *inadequate* evidence to evaluate the potential association between blood Pb and

- Reproductive Endpoints:
  - Stillbirth
  - Endocrine Effects
  - Congenital Malformations
- Few studies at any blood Pb level
- Inconsistent results

The NTP's Conclusions for Reproductive and Developmental Effects

There is *sufficient* evidence that blood Pb levels <10µg/dL are associated with adverse health effects on development in children and reproduction in adult women.

Specific Reproductive and Developmental Charge Questions

i. Please comment on whether the scientific evidence presented supports the NTP's conclusions.

ii. Please comment on whether you agree/disagree with the NTP's conclusions. Explain why. Identify any references that should be cited.

a. Puberty and postnatal growth

b. Sperm parameters and fertility / delayed conception time

c. Spontaneous abortion and stillbirth

d. Fetal growth and lower birth weight

e. Preterm birth and gestational age

f. Endocrine effects and birth effects

Table 8.6: NTP conclusions on reproductive and developmental effects of low-level Pb part 1

Health Effect	Population or Exposure window	NTP Conclusion	Blood Pb Evidence	Bone Pb Evidence
Delayed Puberty	Prenatal	*Inadequate*	No data	No data
	Children	*Sufficient*	Yes, <10µg/dL	No data
		Limited	Yes, <5µg/dL	
Postnatal Growth	Prenatal	*Limited*	Yes, <10µg/dL	one study
	Children	*Sufficient*	Yes, <10µg/dL	one study, no evidence of assoc.
Sperm parameters	Children	*Inadequate*	No data	No data
	Men	*Sufficient*	Yes, ≥15µg/dL	No data
Fertility / Delayed conception time	Men –time to conception	*Sufficient*	Yes, ≥20µg/dL	No data
	Men - fertility	*Limited*	Yes, ≥10µg/dL (1 study)	No data
	Women	*Inadequate*	Unclear	No data

Table 8.6: NTP conclusions on reproductive and developmental effects of low-level Pb part 2				
Health Effect	**Population or Exposure window**	**NTP Conclusion**	**Blood Pb Evidence**	**Bone Pb Evidence**
Spontaneous Abortion	Men	*Limited*	Yes, >31µg/dL	No data
	Women	*Limited*	Yes, <10µg/dL	No data
Stillbirth	Adults	*Inadequate*	Unclear	No data
Reduced Fetal Growth and Lower Birth Weight	Men	*Inadequate*	Unclear	No data
	Women	*Sufficient*	Yes, <10µg/dL	Yes, tibia
Preterm Birth and Gestational Age	Men	*Inadequate*	Unclear	No data
	Women	*Limited*	Yes, <10µg/dL	No data
Endocrine effects	Adults	*Inadequate*	Unclear	one study
Birth Defects	Adults	*Inadequate*	Unclear	No data

e. Other reproductive or developmental effects

i. Please comment on whether there are additional reproductive or developmental effects in humans that may be adversely affected by low-level Pb exposure that you would recommend adding to the document.

Please comment on whether and how the additional reproductive or developmental effects would affect the overall conclusions for health effects associated with blood Pb levels <10µg/dL.

A. General Questions

1) Is the text in the draft monograph articulated clearly and correctly? Are the summary sections useful? Are the tabular information and format easily understandable? If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

2) Is the information in the draft monograph's text and tables presented objectively?
If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.